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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Rajeev JAIN *et al.*

Title: CONTROLLED RELEASE NANOPARTICULATE COMPOSITIONS

Appl. No.: 09/337,675

Filing Date: June 22, 1999

Examiner: Amy E. Pulliam

Art Unit: 1615

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
Washington, D.C. 20231

Sir:

The undersigned, Rajeev A. Jain, hereby declares as follows:

1. I received my Ph.D. degree in 1998 from the University of Rhode Island in Pharmaceutical Sciences. I have been working in the field of drug nanoparticle technology since February 1998, when I joined NanoSystems LLC. This business was then sold and became known as Elan Drug Delivery.

2. Currently I am a Senior Associate at Elan Drug Delivery, with offices at 3000 Horizon Drive, King of Prussia, PA 19406.

3. I am an inventor of the above-referenced application for "Controlled Release of Nanoparticulate Compositions."

4. I submit this declaration to establish that the pending claims of the present application are not obvious in view of U.S. Patent No. 5,145,684 to Liversidge et al.

5. I understand that the Examiner has cited this patent against the application in Office Actions dated July 23, 2002, April 10, 2001, and August 29, 2000. In that regard, I understand the Examiner's position to be that some of the surface stabilizers taught by

Liversidge et al. can function as rate-controlling polymers, thereby allegedly rendering controlled release nanoparticulate drug compositions an obvious invention.

6. I disagree with the Examiner's position. By design, the nanoparticulate drug compositions of Liversidge et al. allow for rapid dissolution and, therefore, rapid onset of drug action. This is because the rate of a drug's dissolution generally directly correlates with surface area. Accordingly, the development of controlled release nanoparticulate drug formulations was surprisingly unexpected.

7. I describe two examples below, which demonstrate a stark contrast between the rapid release of nanoparticulate drug compositions taught by Liversidge et al., and those presently claimed.

EXAMPLE 1 - A DELAYED/PULSATILE RELEASE SYSTEM

8. An immediate release formulation (per Liversidge et al.) and a delayed release formulation (per the present invention) of the drug Compound A were prepared. In an acid environment like that of the stomach, the immediate release formulation rapidly released the drug, which means the drug would immediately become available upon ingestion by a patient. By contrast, the delayed release formulation survived, essentially intact, for two hours in a highly acidic environment. The delayed release formulation would release the drug in a pH environment approximating that of the small intestine. Thus, drug in the delayed release formulation would not become available until passing through a patient's stomach and into the small intestine.

9. To make the immediate release formulation, a colloidal dispersion of nanoparticulate drug and Plasdone K29/32 (polyvinyl pyrrolidone; PVP) as a surface stabilizer was first prepared. The drug in the dispersion had a mean particle size of 189 nm, with 90% of the drug particles below 249 nm, and 100% of the drug particles below 1 micron. The colloidal drug dispersion was converted to a Coating Feed Dispersion by the addition of DOSS and mannitol. The Coating Feed Dispersion was then bottom-sprayed onto 45/60 Paulaur sugar beads (Paulaur Corp., Cranbury, NJ) using a Vector Multi-1 fluid bed

system equipped with a 6" Wuster insert to produce immediate release beads. The final composition of the immediate release beads is shown below in Table 1.

10. To make the delayed release formulation, a portion of immediate release beads was subcoated using an aqueous polyvinyl pyrrolidone (PVP) solution. They then were coated with an aqueous dispersion of polyvinyl acetate phthalate (PVAP) (Sureteric; Colorcon) to produce delayed release beads. The PVP sub-coating formed a barrier between the nanoparticulate drug (from the immediate release coating) and the enteric polymer, PVAP. This avoided any potential incompatibility between the two. The final composition of the delayed release beads is shown below in Table 1.

Table 1- Composition of the Immediate Release and Delayed Release Beads

Ingredients	**Composition of Immediate Release Beads**		**Composition of Delayed Release Beads**	
	grams	**%w/w**	**grams**	**%w/w**
Compound A	700.0	62.4	62.4	44.6
Plasdone K29/32, USP	140.0	12.5	17.5	12.5
Mannitol, USP	140.0	12.5	12.5	8.9
DOSS, USP	42.0	3.7	3.7	2.6
Purified Water, USP	-	-	-	-
45/60 Sugar Spheres NF	100	8.9	8.9	6.4
Polyvinyl acetate phthalate USP (Sureteric)	-	-	35	25.0
Total	**1122.0**	**100.0**	**155.0**	**100.0**

11. The particle size was measured for the delayed release composition following redispersion in an aqueous environment having a pH of 6.5, and for the immediate release composition in aqueous 0.01N HCl and 0.1M NaCl. An electrolyte concentration of 0.01N HCl simulates typical acidic conditions found in the stomach. The 0.1 M NaCl solution simulates the electrolyte concentration found throughout the body, including the intestine.

12. The results of the redispersion test are shown below in Table 2. Essentially all of the drug particles in both types of beads were less than 1000 nm in diameter following redispersion. Average particle sizes were on the order of 240-340 nm. "D90" in the table refers the particle size below which 90% of the drug particles in the composition fall.

Table 2 - Particle Size Analysis of the IR and DR Beads

Sample/Media	Particle Size		
	Mean (nm)	**D90 (nm)**	**% < 1000 nm**
nanoparticulate drug dispersion/DI Water	189	249	100
DR Beads/ pH 6.5 (filtered)	242	345	100
IR Beads/0.01N HCl	280	402	100
IR Beads/0.1M NaCl	338	533	98.5

13. In addition to demonstrating complete redispersion of the component nanoparticulate drug composition, the following data show that upon exposure to a strong acid environment, such as that in the stomach, the immediate release beads entirely released the drug in less than one hour. (See Table 3, column 1, below).

14. By contrast, the delayed release beads would survive the acidic environment of the stomach, and release drug at pH greater than or equal to 6.0. This is demonstrated by the data below showing that the delayed release beads remained over 95% intact after two hours at acidic conditions. (See Table 4, below). However, upon exposure to a basic environment (pH 6.5), they entirely released the drug in less than one hour. (See Table 3, col. 2, below).

Table 3 - Assay of the Immediate Release and Delayed Release beads that were filled into capsules

Lot	Immediate Release Beads % Release at pH 1.2	Delayed Release Beads % Release at pH 6.5
1	102.4	106.8
2	102.5	106.9
3	102.3	106.4
Mean	102.4	106.7

Table 4 - Integrity Analysis of DR Coated Beads

Integrity Analysis (%w/w) - % Release at pH 1.5-2.0			
Time (hr)	**Vessel 1**	**Vessel 2**	**Vessel 3**
2	4.8	4.4	4.3
2	4.8	4.4	4.3
Mean	4.8	4.4	4.3

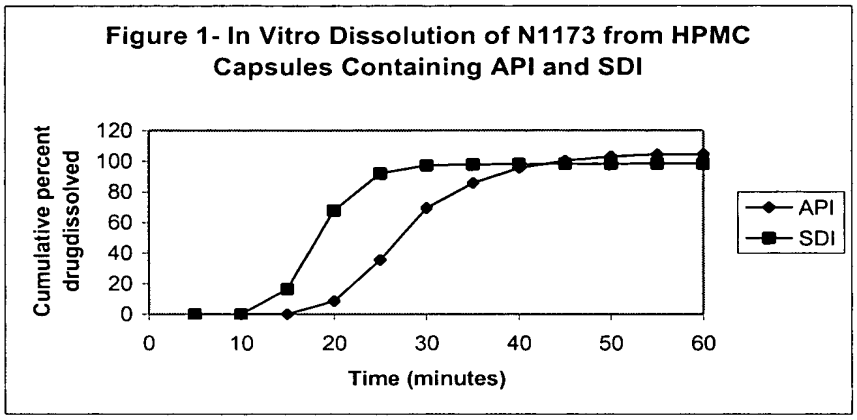
EXAMPLE 2 - AN EXTENDED RELEASE SYSTEM

15. An immediate release formulation (per Liversidge et al.) and an extended release formulation (per the present invention) of the drug Compound B were prepared. In *in vitro* simulations, the immediate release formulation completely dissolved within 30 minutes. By contrast, the extended release formulation slowly dissolved over the course of 20 hours.

16. The immediate release formulation was prepared by spray drying a nanoparticulate drug colloidal dispersion containing 30% drug and two surface stabilizers: 6% polyvinyl pyrrolidone and 0.15 % sodium lauryl sulfate. The spray dried powder was then hand filled into hydroxypropyl methyl cellulose capsules.

17. Figure 1, below, presents the results of an *in vitro* dissolution test in a 1% polysorbate 80/phosphate buffer (USP Method II) using the spray dried immediate release formulation (SDI). Active pharmaceutical ingredient (API) represents a non-nanoparticulate, micronized form of the drug. The results show that the nanoparticulate SDI rapidly dissolved

as compared to the conventional micronized form of the drug. Figure 1 underscores the point that, upon ingestion, nanoparticulate drug formulations generally effect an immediate or rapid drug release due to their relative large surface area.



18. The extended release formulation was prepared by compressing the immediate release nanoparticulate SDI formulation into a controlled release matrix with hydroxypropyl methylcellulose and hydroxypropyl cellulose. These cellulose ethers are commonly employed for oral controlled delivery. Drug release from these matrices results from a glassy-rubbery transition following entry of water into the matrix, and a water-polymer-drug interaction. On coming into contact with aqueous media, matrix tablets prepared using these polymers (hydrogels) swell and form a gel layer at their surface. Water-soluble drugs diffuse out through the gel layer, while poorly water soluble drugs, such as Compound B, are released as a result of erosion of the gel barrier.

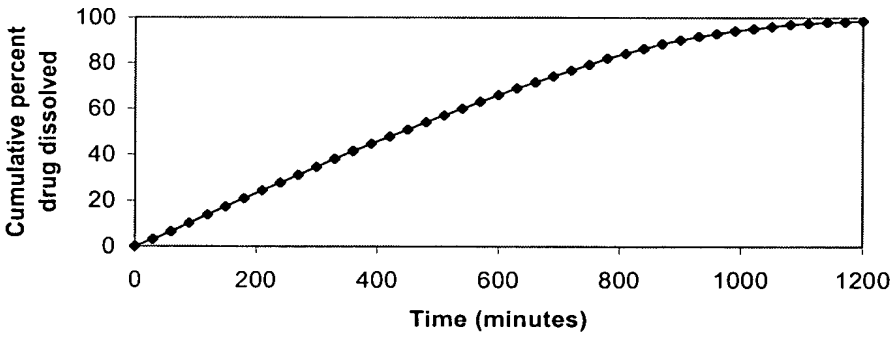
19. Table 5 presents the composition of extended release tablets used in this experiment.

Table 5 - Composition of Extended Release Tablets

Ingredient	Quantity (mg/tablet)
Compound B nanoparticulate SDI	241
Lactose Monoydrate, USP	226.1
Hydroxypropyl Methylcellulose, USP (Methocel K100LV)	162.5
Hydroxypropyl Methylcellulose, USP (Methocel K3LV)	40.6
Magnesium stearate, USP/NF	6.77

20. Figure 2 presents the *in vitro* dissolution profile of the extended release Compound B nanoparticulate drug formulation in 1% polysorbate 80/phosphate buffer (USP Method II). The difference, relative to the immediate release formulation, is dramatic. Whereas the immediate release formulation completely dissolved within 30 minutes, the extended release formulation dissolved over a period of 20 hours, indicating an extended release profile.

Figure 2 - In Vitro Dissolution Profile of Compound B from 200 mg Dose Extended Release Hydrophilic Matrix Tablets



21. Given the differences in formulation and result between the nanoparticulate compositions of Liversidge et al. and the controlled release nanoparticulate compositions of the presently claimed invention, the presently claimed invention cannot be considered

obvious. The incorporation of nanoparticulate drugs into controlled release formulations was unexpected, and provided surprising results.

22. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Inventor:

Full name of inventor _____

Inventor's Signature _____

Date _____ Country of Citizenship _____

Residence _____

Post Office Address _____

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